UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,456	01/14/2002	Claudine Elvire Marie Bruck	BC45225	4140

20462 7590 02/09/2005

SMITHKLINE BEECHAM CORPORATION
CORPORATE INTELLECTUAL PROPERTY-US, UW2220
P. O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

EXAMINER	
YU, MISOOK	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,456	BRUCK ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-37,43-53 and 55-63* is/are pending in the application.

4a) Of the above claim(s) *44-53 and 58-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-37 and 55-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/12/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Claims 43-53, and 58-63 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 35-37, 43-53, and 55-63 are pending. Claims 35-37 and 55-57 are under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification, withdrawn

The objection of specification is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 112

The rejection of claims under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is **withdrawn** in view of the amendment.

Claims 35, 36, and 55-57 **remain rejected** under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This written description rejection is made because claims 35, 36, 54-57 are interpreted as drawn to genus of proteins with various degree of variations (at least 90 to 95 % sequence identity) from SEQ ID NO:2, wherein said genus when administered to a subject induces an immune response that recognizes a polypeptide having the sequence of SEQ ID NO:2.

Applicant argues that "[t]he recited function is a function of the recited polypeptides, not the T-cell or antibodies that may be induced by them" (see the page 10, last line of 1st paragraph of the amendment filed on 11/12/04). This argument has been fully considered but found unpersuasive. The recited function is not enough for the partial structure in the form of percent identity.

As stated in the prior Office action, the recited function "inducing immune response" occurs with other unrelated proteins to instant SEQ ID NO:2. In other words, the structure and the function are not correlated. Any peptides or protein could induce the recited function. Therefore, the limitation "wherein the isolated polypeptide, when administered to a subject in a suitable composition which can include an adjuvant or a suitable carrier coupled to the polypeptide, induces an immune response that recognizes a polypeptide having the sequence of SEQ ID NO:2" is not the function coupled to the structure of the claimed genus. Whether an antibody or a cytotoxic T cell (CTL) binds to a polypeptide would depend on the structure of said polypeptide. Thus, the limitation "wherein the isolated polypeptide, when administered to a subject in a suitable composition which can include an adjuvant or a suitable carrier coupled to the polypeptide, induces an immune response that recognizes a polypeptide having the

sequence of SEQ ID NO:2" appears to be anther way of describing the structure of claimed polypeptides, not the function of the claimed polypeptide because antibodies or activated T cells bind to a polypeptide based on structure (epitope), not based on function of a polypeptide. Note Figure 3.1 (page 41) of Benjamini and Leskowitz (1991, Immunology, A Short Course, Wiley-Liss, Chapter 3, pages 37-45 only).

Claims 38, 39-41, and 54-57 depend on the rejected base claim 35, and the limitations in the dependent claims do not resolve lack of written description of the base claim, therefore rejected for the same reason stated for the base claim 35.

Claims 35-37, and 55-57 **remain rejected** under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making antibodies in a non-human subject, does not reasonably provide enablement for inducing immune response in a human subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use and make the invention commensurate in scope with these claims. This rejection has multiple aspects.

This scope of enablement rejection is made because the nature of the claimed invention is interpreted as drawn to SEQ ID NO:2 or similar variants for inducing an immune response in a human subject.

Applicant argues that the Office cites exceptions instead of norm in terms of protein expression and those specific cases do not apply to all cases. This argument has been fully considered but found unpersuasive.

As noted before in the previous Office action, the specification discloses:

1) Overexpression of CASB168 mRNA (corresponding cDNA is SEQ ID NO:1 according to page 6-9) in colon samples from colon cancer patients as compared to normal control, is detected using real-time PCR (note at pages 34).
2) SEQ ID NO:1 is a full-length cDNA encoding a putative protein, SEQ ID NO:2 (note line 21 of page 37).
3) Putative HLA-A binding peptides derived from SEQ ID NO:2 at pages 43-45.

One cannot extrapolate the teaching of the specification to the claimed invention because the specification does not teach how to induce SEQ ID NO:2-specific immune response in a human subject using the claimed polypeptides. The specification provides no exemplification of or guidance on how to use the claimed genus to induce either B- or T-cell mediated immune response in a human subject. The specification does not disclose common structural attributes that stimulate an immune response in a subject that the claimed genus is from. There is insufficient guidance regarding the parameters and sequence of peptides that correlate with the ability to stimulate T cells and generate CTLs with claimed specifity/activity. There is insufficient guidance regarding selection of peptides that meet the instant criteria of stimulating an immune response. The specification at page 43-45 discloses putative HLA-A binding peptides derived from SEQ ID NO:2. However, the specification does not teach which(s) fragment of the numerous SEQ ID NO:2 fragments listed in the specification at pages

43-45 or other claimed peptides in the instant claims can be used to stimulate immune response in vivo human subject.

First, the specification does not even establish whether SEQ ID NO:2 is a cancer antigen, let alone how to induce either cell-mediated or antibody-mediated immune response against SEQ ID NO:2. The specification does not teach any biological or biochemical activity of SEQ ID NO:2. It is a newly discovered putative protein encoded by a human gene (note page 37 line 21). Although the instant application implies that SEQ ID NO:2 might be a human cancer antigen based on the mRNA expression data in colon cancer samples (see the summary above), the specification does not disclose whether the protein overexpression is correlated with any in vivo tumor growth. The art recognizes that expression of mRNA does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following

exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. For the above reasons, one of skill in the art would not be able to assume over-expression of SEQ ID NO:2 is associated with colon cancers.

Even if SEQ ID NO:2 is determined to be a colon cancer antigen, inducing an immune response against a cancer antigen that is also expressed in normal cells is not a trivial matter in the state of art. The relative skill in the art is low.

Riott et al., (Immunology, Fourth Edition, 1996, Mosby, pages 7.8-7.12, and Chapter 10 only) review that the immune system has two ways of responding to an antigen, in the instant case, SEQ ID NO:2, a putative colon cancer antigen based on the corresponding mRNA expression data. The first is the antibody-mediated response by which the immune system operates to destroy the antigen, and the second is the "cell-mediated" response, in which T cells recognizes cell-bound antigen in association with MHC molecules. MHC class I and class II act as guidance systems for T cells. This is known as MHC restriction. Only a minority of peptide fragments from a protein antigen is able to bind particular MHC molecules. Different MHC molecules bind different sets of peptides. Riott et al., teach at Fig. 7.22 and Fig. 7.23, and also page 7.10, right

column that the peptides sizes 12-15 are optimal for MHC molecule class I and certain amino acids at certain positions are critical for binding to MHC class I.

US Pat. 5,840,839 (Nov. 24, 1998) teaches at column 19 that finding peptides that bind a MHC molecule and stimulate an immune response, is not a trivial matter. The '839 patent at column 19, lines 53 to 67 teaches that structure of a T cell epitope that stimulates an immune response in context of MHC molecules is unpredictable in the current state of art. The '839 patent at columns 19-20, and Table 1 teaches that the various candidate T cell epitopes selected based on theoretical binding motif of one class of MHC molecule, i.e. HLA-A31 do not work when they are experimentally tested as shown in Table 1. This suggests that theoretically selected T cell binding motifs as disclosed at pages 43-45 of the instant specification have to be tested experimentally in order to determine whether they are actually T cell epitopes or not.

The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. Ezzell (J. NIH Res, 1995, 7:46-49) teaches that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10: 1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer

vaccines and you're likely to get the following response: cancer vaccines don't work. Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1). Furthermore, Boon (Adv Can Res, 1992, 58:177-210) teaches even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph).

As for B-cell mediated immune response part of enablement rejection, Benjamini and Leskowitz (cited above) at page 38, first sentence under the heading "Foreignness" teach "Animals normally do not respond immunologically to self." Thus, it is highly unlikely that instant SEQ ID NO:2 or similar proteins would induce any B-cell mediated immune response against SEQ ID NO:2 or similar proteins in a human subject.

The specification provides insufficient guidance with regard to theses issues and provides no working examples of a peptide that would work with any MHC molecule in inducing an immune response in a human subject. Considering the state of art, the broad scope of claims in respect to the nature of peptide and also to the nature of MHC molecules, it is concluded that that undue experimentation is required to practice the full scope of the claimed invention. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves.

Presenting scientific data demonstrating that the instantly claimed protein expression is over-expressed in cancer would obviate this rejection.

Claim Rejections - 35 USC § 101, Maintained

Claims 35-37, and 55-57 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility.

This utility rejection is made because the claims 35-42, and 54-57 are interpreted as drawn to the newly discovered polypeptide, SEQ ID NO:2 and similar variants. The asserted utility in inducing cell-mediated immune response is not substantial because the specification does not even establish whether SEQ ID NO:2 is a cancer antigen, let alone how to induce either cell-mediated or antibody-mediated immune response against SEQ ID NO:2.

Applicant argues with the mRNA expression data. This argument is not commensurate in scope of the claims. The claims are not drawn to nucleic acids. As noted above under 112, first paragraph, this rejection would also be obviated by presenting scientific data demonstrating that the instantly claimed protein expression is over-expressed in cancer.

Claim Rejections - 35 USC § 102, Withdrawn

The rejection of claims under 35 U.S.C. 102(b) as being anticipated by Mankovich et al., (1989, Journal of Bacteriology, vol. 171, pages 5325-31) as evidenced by Benjamini and Leskowitz (1991, Immunology, A Short Course, Wiley-Liss, Chapter 3, pages 37-45 only) is withdrawn because the amended claims are no longer anticipated by the art of record.

Claim Rejections - 35 USC § 103, Withdrawn

The rejection of the claims under 35 U.S.C. 103(a) as being unpatentable over Mankovich et al., (1989, Journal of Bacteriology, vol. 171, pages 5325-31) in view of WO 95/17210 (29 June 1995) is withdrawn in view of the amendment.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
2/7/05